REMARKS

Claim Amendments

Claims 114, 122, 130, 138, 146, 148, 150, 190, 199, 208, 217, 226, 229 and 232 have been amended to specify that the reference RNA sequence and the (selected) target viral RNA sequence "can be amplified by the same oligonucleotides or by different oligonucleotides." Support for this amendment can be found in the disclosure in the present application in which the reference RNA is a maxigene construct (see page 6, lines 15-21) or a different RNA construct (see, e.g., original claim 26).

Applicants submit that these amendments do not constitute new matter and their entry is requested.

Summary of the Claims

The claims comprise two sets of claims, each directed to one of the reference RNA sequences. These sets of claims are summarized as follows.

Claims 114-151 and 235-241 are directed to processes for quantitation of a target viral RNA sequence in a sample, an amplification reaction mixture (claims 146-147 and 239), a reverse transcription reaction mixture (claims 148-149 and 240) and a kit (claims 150-151 and 241). The process involve the simultaneous amplification of a target viral RNA sequence and reference RNA sequence (claims 114-121, 130-137, 235 and 237) or involve first a simultaneous reverse transcription and then a simultaneous amplification of a target viral RNA sequence and reference RNA sequence (claims 122-129, 138-145, 236 and 238). The reference RNA sequence of claims 114-151 is a reference RNA sequence that consists of the target viral RNA sequence with a multibase insert into a site within the target viral RNA sequence. The reference RNA sequence and the target RNA sequence can be amplified by the same oligonucleotides or by different oligonucleotides.

Claims 190-234 and 242-248 are directed to processes for quantitation of a target viral RNA sequence in a sample, an amplification reaction mixture (claims 226-228 and 246), a reverse transcription reaction mixture (claims 229-231 and 247) and a kit (claims 232-234 and 248). The process involve the simultaneous amplification of a target viral RNA sequence and

reference RNA sequence (claims 190-198, 208-216, 242 and 244) or involve first a simultaneous reverse transcription and then a simultaneous amplification of a target viral RNA sequence and reference RNA sequence (claims 199-207, 217-225, 243 and 245). The reference RNA sequence of claims 190-234 is a reference RNA sequence that comprises a sequence present in the target viral RNA sequence and a sequence that is not present in the target viral RNA sequence. The reference RNA sequence and the target RNA sequence can be amplified by the same oligonucleotides or by different oligonucleotides.

Summary of the Invention

The present invention is directed to a method for the quantitation of target viral RNA in a sample by simultaneously amplifying a target viral RNA sequence and a known quantity of a reference RNA sequence as an internal standard. That is, the target viral RNA sequence, if present, and the reference sequence are simultaneously amplified in the same reaction mixture. The quantity of target viral RNA present in the sample is determined by comparing the amount of the amplified target viral RNA and the amount of the amplified reference RNA based on the known quantity of reference RNA added as an internal control. The reference RNA sequence may be (a) a reference RNA sequence that consists of the target viral RNA sequence with a multibase insert into a site within the target viral RNA sequence or (b) a reference RNA sequence that comprises a sequence present in the target viral RNA sequence and a sequence that is not present in the target viral RNA sequence. In each instance, the reference RNA sequence and the target viral RNA sequence are of similar length and can be amplified by the same oligonucleotides or by different oligonucleotides.

Priority

According to the first paragraph of the specification, the present application is a continuation-in-part of three applications, Serial No. 07/355,296, filed 22 May 1989, Serial No. 07/143,045, filed 12 January 1988 and Serial No. 07/148,959, filed 27 January 1988. Thus, the present application claims priority to each of these three applications. Applicants submit that they are entitled to a priority date of at least 27 January 1988 for the amended claims for the

same reasons as set forth in the Amendment filed on 18 April 2007, as well as the disclosure in Serial No. 07/148,959 of the simultaneous amplification of target viral RNA with various other RNA sequences.

Examiner's Claim Analysis

In the Office Action dated 6 June 2007, the Examiner contends that the "claims were amended to **require** that the reference RNA and target RNA sequences are of similar length and amplified by the same primers." (Office Action, p. 2; emphasis added) As the Examiner correctly stated, these claims must be analyzed in light of the decision by the Board of Patent Appeals and Interferences (BPAI) in Interference 105,055. The Examiner then presents a brief analysis of the BPAI's decision on Murakawa preliminary motion 1 (Decision on Preliminary Motion, Paper 47 in Patent Interference No. 105,055). The Examiner concluded that the express difference between the Wang claims and the Murakawa claim as presented in Murakawa preliminary motion 1 was that Wang requires the use of primers that can amplify both the reference and the target sequences and Murakawa did not. Thus, the Examiner concludes that the claim limitation that "**requires** the use of primers that can amplify both the reference and target sequences renders the claims unpatentable under 35 U.S.C. § 135(b) and 35 U.S.C. § 103 over Wang et al. (US 5,219,727), since the claims are now prior art relative to one another." (Office Action, p. 3; emphasis added) In addressing the argument made by Applicants in the Amendment filed on 18 April 2007, the Examiner contended that Applicants "incorrectly analyzes the BPAI decision." (Office Action, p. 3) However, the decision referred to by the Examiner in this Office Action is not the decision that Applicants analyzed in the prior amendment. As fully set forth below, Applicants submit that they correctly analyzed the BPAI decision, namely, the BPAI's decision on Wang preliminary motion 1. Applicants submit that this decision is controlling on the issue of the application of 35 U.S.C. § 135(b) to the present claims

Rejection Over Wang et al.

In the Office Action dated 6 June 2007, the Examiner rejected claims 114, 115, 117, 118, 120, 122, 123, 125, 126, 128, 130, 131, 133, 134, 136, 138, 141, 142, 144, 146-151, 190-192, 194, 195, 197, 199-201, 203, 204, 206, 208-210, 212, 213, 215, 217-219, 221, 222, 224 and 226-248 under 35 U.S.C. § 135(b) over Wang et al. (US 5,219,727). Applicants do not generally disagree with the Examiner's analysis of Wang et al. However, Applicants submit that the claimed subject matter **does not require** the use of a shared primer pair, as was held by the BPAI in Interference No. 105,055. Since the claimed subject matter **does not require** the use of a shared primer pair, Wang et al. is not prior art under 35 U.S.C. § 135(b).

As noted above, Applicants submit that the BPAI decision on Wang preliminary motion 1 is controlling on the issue of whether the claimed subject matter, particularly the language presented in the prior amendment, i.e., amplified and detected by the same oligonucleotides, claims the same subject matter as Wang et al. A copy of the BPAI decision on Wang preliminary motion 1 (titled Memorandum Opinion and Order) is attached for the convenience of the Examiner.

The issue with respect to Wang preliminary motion 1 was whether the Murakawa et al. application contained a claim that had been presented less than one year after the grant of the Wang et al. patent that was the same as, or for the same or substantially the same subject matter as, a claim of the Wang et al. patent. If Murakawa et al. had presented such a claim, then the claim would not be barred under 35 U.S.C. § 135(b). As the BPAI stated in its decision on Wang preliminary motion 1, a later filed claim does not differ from an earlier claim if it contains the same material limitations. If all of the material limitations of the copied claim are present in, or necessarily result from, the limitations of earlier claims, then the copied claim satisfies 35 U.S.C. § 135(b). The Wang et al. claims copied by Murakawa et al. were analyzed by the BPAI in accordance with these principles.

In its analysis of the Wang et al. claims, the BPAI held that they contained two material limitations, i.e., (a) the use of a predetermined initial amount of a control sequence and (b) the use of a shared primer pair for amplifying the control and target sequences. (Memorandum Opinion and Order, pp. 5-9) The BPAI found that the Murakawa et al. earlier claims contained

the first limitation, i.e., the use of a predetermined initial amount of a control sequence. (Memorandum Opinion and Order, pp. 9-13) However, the BPAI found that the Murakwa et al. earlier claims did not require or necessarily result in use of a shared primer pair for amplifying control and target sequences. (Memorandum Opinion and Order, pp. 13-25)

Specifically, Murakawa et al. argued in response to the Wang preliminary motion 1 that the language of the earlier claims, particularly language concerning a control sequence that includes substantially more nucleotides than the target sequence, when read in light of the specification by a skilled artisan necessarily results in, i.e., requires, the use of a shared primer pair. This argument was analyzed by the BPAI in its decision. (Memorandum Opinion and Order, pp. 13-25) The BPAI considered whether simultaneously subjecting a sample and any of three possible control sequences to PCR amplification under conditions to simultaneously amplify a target sequence and a control sequence necessarily results in or requires use of shared primer pairs. The BPAI first concluded that the Murakawa et al. earlier claims did not exclude the use of shared primer pairs. (Memorandum Opinion and Order, pp. 16-17) However, the issue was whether the language of the claims required or necessarily resulted in the use of shared primer pairs.

The BPAI considered each of the three possible control sequences and concluded that the Murakawa et al. earlier claims did not require or necessarily result in use of shared primer pairs. (Memorandum Opinion and Order, pp. 17-23) The BPAI concluded that a control sequence comprising a multi-base insertion does not require an insertion preselected to preserve the primer binding sites and thus did not require or necessarily result in the use of a shared primer pair, although it could encompass a shared primer pair. (Memorandum Opinion and Order, pp. 18-20) Murakawa et al. argued that the specification disclosed a maxigene (i.e., control sequence with multi-base insert) that could be "amplified and detected by the same oligonucleotides" used for the target sequence. The specification further disclosed an example in which the multibase insert was inserted into a preselected site between primer binding sites of the target sequence. The BPAI concluded that it was impermissible to limit the claimed subject matter to a preferred embodiment and thus the preselected language did not provide basis for requiring or necessarily resulting in use of a shared primer pair. (Memorandum Opinion and Order, p. 20)

In its analysis, the BPAI then stated "the dispositive question is whether 'a reference RNA which **can be amplified and detected by the same oligonucleotides** as used for authentic virus RNA samples' necessarily **requires** or results in the use of a shared primer pair." (Memorandum Opinion and Order, p. 20; emphasis added) The BPAI concluded that there was no disclosure in the specification that the preselected site should be chosen to avoid disrupting primer binding sites. (Memorandum Opinion and Order, pp. 21-22) Thus, the BPAI concluded that although the Murakawa et al. earlier claims "encompass use of a shared primer pair, they **do not require** or necessarily result in use of a shared primer pair." (Memorandum Opinion and Order, p. 22; emphasis added) In this regard, the BPAI stated "[I]t is possible to have a maxigene control sequence which can be amplified by different primers and detected by the same oligonucleotides used for the target sequence." (Memorandum Opinion and Order, p. 22) The BPAI concluded that "binding to a shared primer pair is **neither excluded, required nor a necessary result**" in any of the Murakawa et al. earlier claims. (Memorandum Opinion and Order, p. 22; emphasis added) Thus, the BPAI concluded that none of the earlier Murakwa claims is directed to the same or substantially the same invention as claimed in Wang et al. (Memorandum Opinion and Order, pp. 22-23) These earlier claims included claims that, when read in light of the specification, include a reference RNA that can be amplified and detected by the same oligonucleotides as the target RNA.

Thus, the BPAI specifically held that the language relied upon by the Examiner in making the rejections in the present Office Action, i.e., "can be amplified and detected by the same oligonucleotides," **did not require** or necessarily result in the use of a shared primer pair. Thus, Applicants submit that the BPAI has held that this language **does not require** the use of a shared primer pair in direct contrast to the Examiner's contention. Because the claims do not require the same primer pair, they are not barred by 35 U.S.C. § 135(b).

In summary, the BPAI found that the subject matter in which the reference and target sequences "can be amplified and detected by the same oligonucleotides" **did not require or necessarily result** in the use of a shared primer pair, i.e., this language **did not require** the use of primers that can amplify both the reference and target sequences. Thus, the BPAI concluded that the same subject matter was not claimed by Murakawa et al. less than one year after the

grant of Wang et al. Since, the BPAI concluded that Murakawa et al.'s claimed subject matter, which included reference RNA sequences that could "be amplified and detected by the same oligonucleotides" as the target RNA sequence, was not the same as Wang et al., Applicants submit that the Murakawa et al. subject matter now being claimed is likewise not the same as Wang et al. and is therefore not barred under 35 U.S.C. § 135(b).

In order to make it clear that the present claims are not directed to the same subject matter as Wang et al., the claims have been amended to make explicit what the BPAI stated in its decision on Wang preliminary motion 1, i.e., that the claim language encompasses the use of the same primers as well as the use of different primers, and thus, as held by the BPAI, the claimed subject matter **does not require** the use of the same primers.

In view of the amendments to the claims and the above remarks, it is submitted that the claimed subject matter is not subject to a rejection under 35 U.S.C. § 135(b) over Wang et al., i.e., it is submitted that Wang et al. is not prior art under 35 U.S.C. § 135(b). Withdrawal of this rejection is requested.

Rejection Over Wang et al. in view of Mullis et al.

In the Office Action dated 6 June 2007, the Examiner rejected claims 116, 119, 121, 124, 127, 129, 132, 135, 137, 139, 140, 143, 145, 193, 196, 198, 202, 205, 207, 211, 214, 220, 223 and 225 under 35 U.S.C. § 135(b) over Wang et al. in view of Mullis et al. (US 4,683,195). As detailed above, the claimed subject matter is not subject to a rejection under 35 U.S.C. § 135(b) over Wang et al. in view of the BPAI decision on Wang preliminary motion 1 (Memorandum Opinion and Order dated 5 November 2003, Paper 36 in Patent Interference No. 105,055). Thus, these rejected claims are patentable over the cited prior art, i.e., they are not properly subject to a rejection under 35 U.S.C. § 135(b) over Wang et al. in view of Mullis et al.

In view of the amendments to the claims and the above remarks, it is submitted that the claimed subject matter is not subject to a rejection under 35 U.S.C. § 135(b) over Wang et al. in view of Mullis et al., i.e., it is submitted that Wang et al. is not prior art under 35 U.S.C. § 135(b) and thus the rejection falls. Withdrawal of this rejection is requested.

Concluding Comments

In view of the above amendments and remarks, it is submitted that the claims are fully supported by the instant application, entitled to a priority date of at least 27 January 1988 and are patentable over the prior art of record. Reconsideration of this application and early notice of allowance is requested. The Examiner is invited to telephone the undersigned if it will assist in expediting the prosecution and allowance of the instant application.

Respectfully submitted,

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Attachment: Memorandum Opinion and Order (BPAI Decision on Wang preliminary motion 1, Paper 36, Patent Interference 105,055, dated 5 November 2003)

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